Claims

What is claimed is:

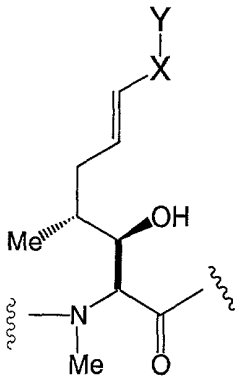
1. A cyclosporin analog of formula I or a pro-drug or a pharmaceutically acceptable salt thereof:

A---B---Sar-MeLeu-Val-MeLeu-Ala---U---MeLeu-MeLeu-MeVal
1 2 8

(I)

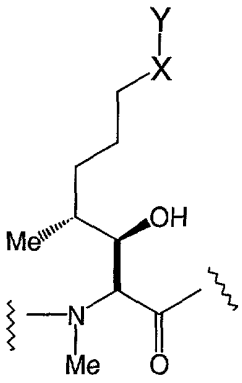
wherein

(i) A is of the formula:



(A1)

or



(A2)

wherein:

X is absent, -C1-C6 alkyl-, or -C3-C6 cycloalkyl-;

Y is selected from the group consisting of: aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

(ii) B is -αAbu-, -Val-, -Thr- or -Nva-; and

(iii) U is -(D)Ala-, -(D)Ser-, -[O-(2-hydroxyethyl)(D)Ser]-, -[O-(acyl)(D)Ser]- or -[O-(2-acyloxyethyl)(D)Ser]-.

2. A cyclosporin analog according to Claim 1 or a pro-drug or a pharmaceutically acceptable salt thereof, wherein in formula I, B is -αAbu-, and U is -(D)Ala-.

3. A cyclosporin analog according to Claim 1 or a pro-drug or a pharmaceutically acceptable salt thereof, wherein in formula I:

(i) A is of the formula A1 or A2, wherein:

X is absent; and

Y is selected from the group consisting of: aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

(ii) B is -αAbu-; and

(iii) U is -(D)Ala-.

4. A cyclosporin analog according to Claim 1 or a pro-drug or a pharmaceutically acceptable salt thereof, selected from the group consisting of:

Compound of formula (I), where A=A1, X is absent and Y = (2'-Me)Ph; B is –αAbu-; and U is –(D)Ala-;

Compound of formula (I), where A=A1, X is absent and Y = (4'-F)Ph; B is –αAbu-; and U is –(D)Ala-;

Compound of formula (I), where A=A1, X is absent and Y = (4'-CF3)Ph; B is –αAbu-; and U is –(D)Ala-;

Compound of formula (I), where A=A1, X is absent and Y = (2'-Br)Ph; B is –αAbu-; and U is –(D)Ala-;

Compound of formula (I), where A=A1, X is absent and Y = (2'-Cl)Ph; B is –αAbu-; and U is –(D)Ala-;

Compound of formula (I), where A=A1, X is absent and Y = (2'-OMe)Ph; B is –αAbu-; and U is –(D)Ala-;

Compound of formula (I), where A=A1, X is absent and Y = (3'-Cl)Ph; B is –αAbu-; and U is –(D)Ala-;

Compound of formula (I), where A=A1, X is absent and Y = (4'-Cl)Ph; B is –αAbu-; and U is –(D)Ala-;

Compound of formula (I), where A=A1, X is absent and Y = (3'-Br)Ph; B is –αAbu-; and U is –(D)Ala-;

Compound of formula (I), where A=A1, X is absent and Y = (4'-Br)Ph; B is –αAbu-; and U is –(D)Ala-;

Compound of formula (I), where A=A1, X is absent and Y = (3'-$COOCH_3$)Ph; B is –αAbu-; and U is –(D)Ala-;

Compound of formula (I), where A=A1, X is absent and Y = (4'-$COOCH_3$)Ph; B is –αAbu-; and U is –(D)Ala-;

Compound of formula (I), where A=A1, X is absent and Y = (2'- Naphthalene); B is –αAbu-; and U is –(D)Ala-;

Compound of formula (I), where A=A1, X is absent and Y = (4'-t-butyl)Ph; B is –αAbu-; and U is –(D)Ala-;

Compound of formula (I), where A=A1, X is absent and Y = (pentafluoro)Ph; B is –αAbu-; and U is –(D)Ala-;

Compound of formula (I), where A=A1, X is absent and Y = (4'-AcO-)Ph; B is –αAbu-; and U is –(D)Ala-;

Compound of formula (I), where A=A1, X is absent and Y = (4'-OCH_3)Ph; B is –αAbu-; and U is –(D)Ala-;

Compound of formula (I), where A=A1, X is absent and Y = (3', 4'-OMe_2)Ph; B is –αAbu-; and U is –(D)Ala-;

Compound of formula (I), where A=A1, X is absent and Y = (2',5'-Me_2)Ph; B is –αAbu-; and U is –(D)Ala-;

Compound of formula (I), where A=A1, X is absent and Y = Pyridine; B is –αAbu; and U is –(D)Ala-;

Compound of formula (I), where A=A1, X is absent and Y = Pyrrole; B is –αAbu; and U is –(D)Ala-;

Compound of formula (I), where A=A1, X is absent and Y = (N-methyl) Pyrrole; B is –αAbu; and U is –(D)Ala-;

Compound of formula (I), where A=A1, X is absent and Y = Thiophene; B is –αAbu; and U is –(D)Ala-;

Compound of formula (I), where A=A1, X is absent and Y = Oxazole; B is –αAbu; and U is –(D)Ala-;

Compound of formula (I), where A=A2, X is absent and Y = (2'-Me)Ph; B is –αAbu; and U is –(D)Ala-;

Compound of formula (I), where A=A1, X is absent and Y = (S)Ph; B is –αAbu; and U is –(D)Ala-;

Compound of formula (I), where A=A1, X is absent and Y = (SO)Ph; B is –αAbu; and U is –(D)Ala-; and

Compound of formula (I), where A=A1, X is absent and Y = (SO_2)Ph; B is –αAbu; and U is –(D)Ala-.

5. A chemical process for preparing a cyclosporin analog of formula I as claimed in Claim 1, comprising reacting a compound of formula I, wherein A= -MeBmt-, with:

a. an olefin of formula CH_2=CH-X-Y, wherein X and Y are as defined in Claim 1, and

b. a catalyst;

in the presence of a lithium salt in an organic solvent and optionally converting the product of said reaction into a pharmaceutically acceptable salt.

6. The process of claim 5, wherein the catalyst is Grubb's ruthenium alkylidene, Grubbs dihydroimidazole ruthenium catalyst, Schrock-Hoveyda molybdenum catalyst, Nolan's catalyst, a benzylidene catalyst or a molybdenum catalyst.

7. A chemical process for preparing a cyclosporin analog of formula I as claimed in Claim 1, comprising:

a. reacting a compound of formula I, wherein A= -MeBmt- with:

i. an olefin of formula CH_2=CH-X-Y, wherein X and Y are as defined in Claim 1; and

ii. a catalyst;

in the presence of a lithium salt in an organic solvent; and

b. hydrogenating the product of step a in an organic solvent under hydrogen with a catalyst;

and optionally converting the product of said reaction into a pharmaceutically acceptable salt.

8. The chemical process as claimed in Claim 7, wherein the catalyst in step (a) (ii) is Grubb's ruthenium alkylidene, Grubbs dihydroimidazole ruthenium catalyst, Schrock-Hoveyda molybdenum catalyst, Nolan's catalyst, a benzylidene catalyst or a molybdenum catalyst.

9. The chemical process as claimed in Claim 7, wherein step (b) is performed at room temperature.

10. The chemical process as claimed in Claim 9, wherein the catalyst in step (b) is Palladium on carbon or Platinum Oxide.

11. A pharmaceutical composition, said composition comprising at least one cyclosporin analog of formula I as claimed in Claim 1, said cyclosporin analog being present alone or in combination with a pharmaceutically acceptable carrier or excipient.

12. A method for treating autoimmune diseases in a subject, which comprises the step of administering to said subject a therapeutically effective amount of at least one cyclosporin analog of formula I as claimed in Claim 1.

13. The method of Claim 12, wherein said autoimmune disease is selected from conical cornea, keratitis, dysophia epithelialis cornea, leukoma, Mooren's ulcer, sclevitis and Grave's ophthalmopathy.

14. A method for preventing organ transplantation rejection in a subject, which comprises the step of administering to said subject a therapeutically effective amount of at least one cyclosporin analog of formula I as claimed in Claim 1.